Complex Generic Drug Products: Development to Assessment

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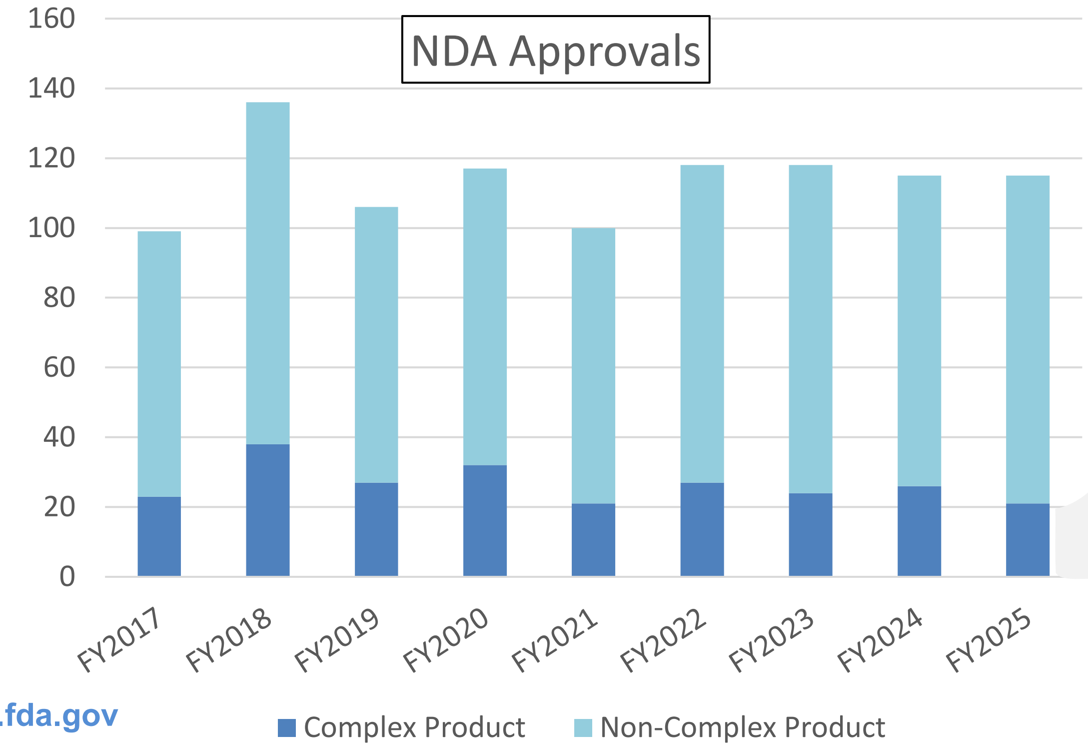
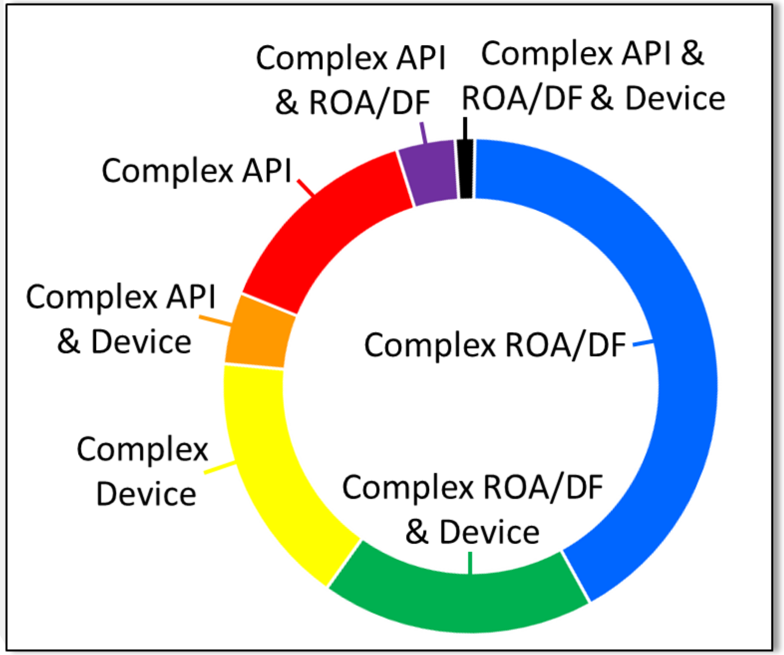
Agenda

- Complex product NDA and ANDA submission and approval metrics
- Facilitating complex product ANDA submissions and approvals:
  - Public workshops and ANDA initiative for early cross-disciplinary coordination
  - Product Specific Guidance (PSG) development and revisions
    - FDA's proactive internal research program, global harmonization efforts, and improving clarity on the type of studies recommended
- Active ingredient sameness recommendations for generic peptide products
- Active ingredient characterization and comparability studies
  - Orthogonal methods
  - Focus: Comparability studies of oligomer/aggregation states
- Comparative physicochemical characterization for generic colloidal iron carbohydrate products

Complex Products & NDA Approvals

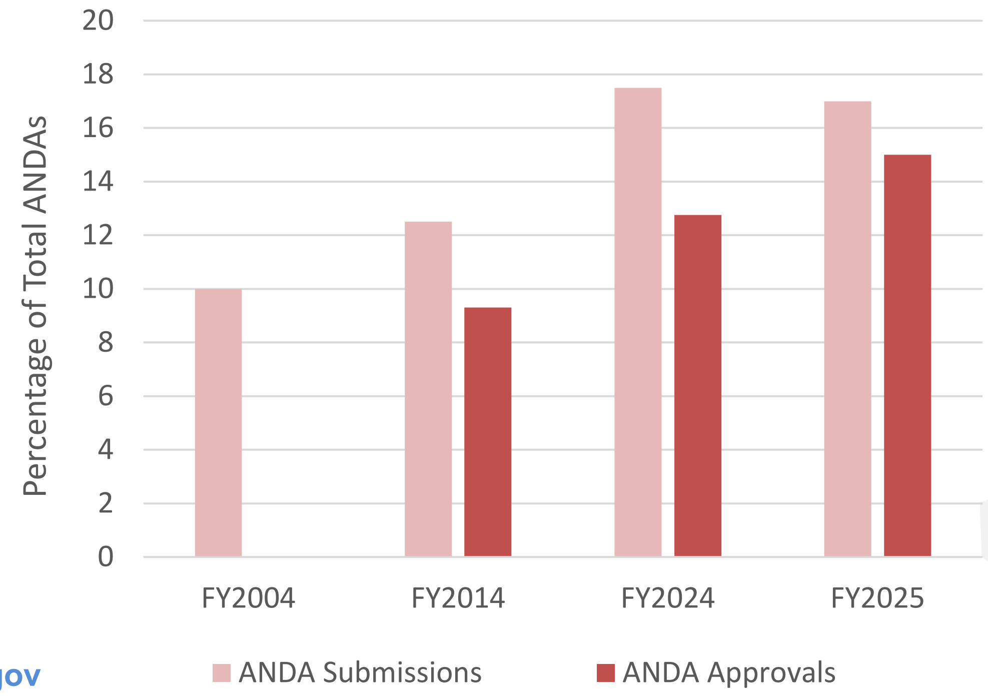
- 2017 GDUFA II commitment letter outlined general criteria for complex product definition.
  - Complex: active ingredient (API), route of delivery (ROA), dosage form (DF), or drug-device combination product (device)
  - [MAPP 5240.10](#) provides details and examples of how products are classified as complex
- Approximately 110 NDAs are approved each year, ~25% of these meet one or more complex product criteria.
  - Per GDUFA III commitments, FDA has goal dates for developing and posting PSGs for NDAs approved on or after Oct 1, 2022.
  - Over 50% of the complex product NDAs approved between FY2017and FY2025 had a complex ROA/DF, ~25% had a complex API

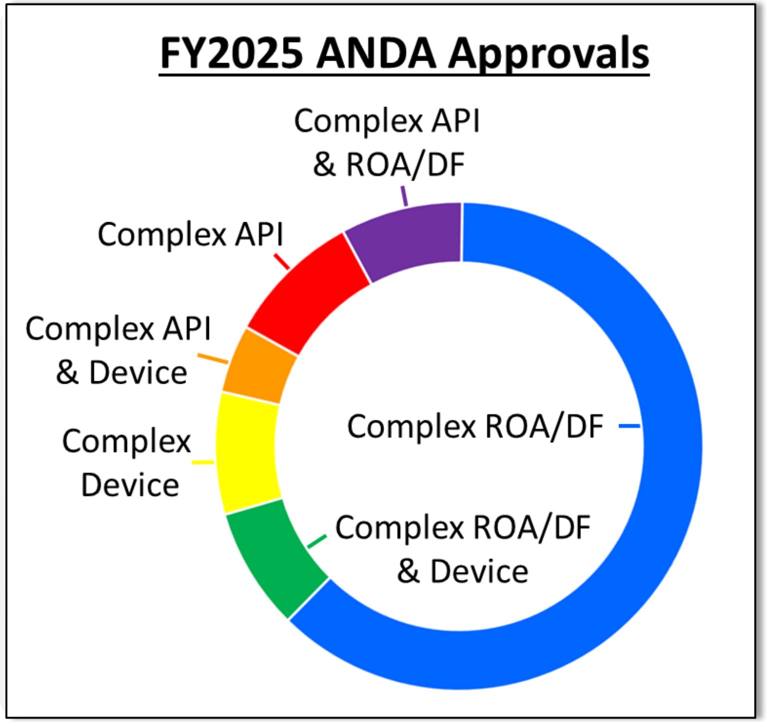




Complex Product ANDA Submissions & Approvals

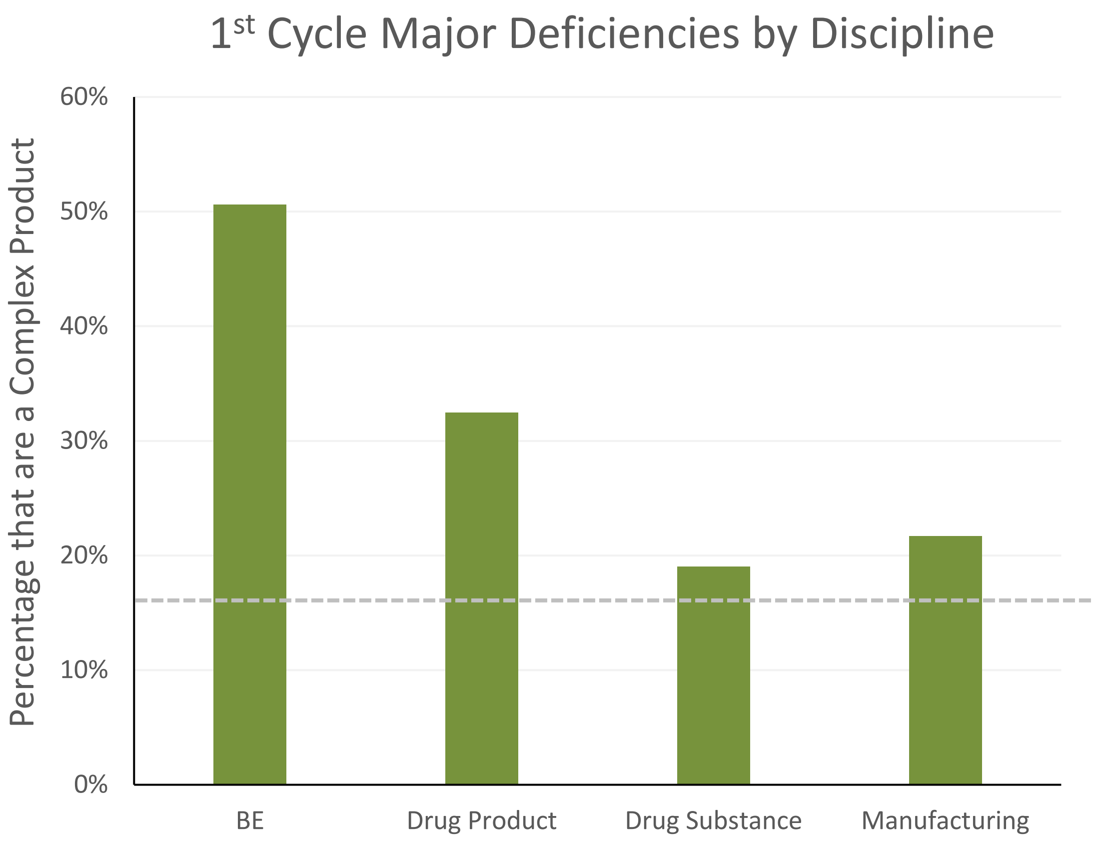
- Complex products typically represent 12-19% of total ANDA submissions and approvals each year, an increase from approximately 10% of ANDA submissions in FY2004.
  - The majority (>75%) of complex ANDA approvals in FY2025 had a complex ROA/DF, ~23% had complex API





ANDA Major Deficiencies: Complex vs Non-Complex Products

- Complex product ANDAs typically have a higher percentage of major bioequivalence (BE) and drug product deficiencies in the first review cycle compared to non-complex product ANDAs.
  - Complex products were ~50% of all major BE and ~33% of all major Drug Product deficiencies issued in the first review cycle even though complex products were only ~17% of the ANDAs.
  - Major Manufacturing or Drug Substance deficiencies do not appear to be dependent on product complexity



Analysis of 1st Cycle complete response letters issued in FY2022

Enhanced Engagement for Complex Product Development

- Initiatives related to GDUFA III Commitments
  - Meetings: Pre-ANDA, midcycle, and post CRL meetings
  - **PSG development and revision**
    - CDER Subject Matter Expert Triage Team (STT)
    - Global harmonization efforts and improving clarity of PSG recommendations
- Examples of other initiatives
  - FDA hosted public workshops and Center for Research on Complex Generics (CRCG):
    - Oct 7-8, 2025: *Advancing Generic Drug Development: Translating Science to Approval*
    - Oct 15-16, 2025: *Modeling and Artificial Intelligence in Generic Drug Development and Product Lifecycle Management*
    - Nov 19-20, 2025: *Visionary Standards: Advancing Science and Regulation in Generic Ophthalmic Products*
  - A proactive triage to identify ANDA submissions that may warrant increased and earlier cross-disciplinary team-based assessment

Subject Matter Expert Triage Team (STT)

- An internal program to **identify and direct research** to support PSG development of complex generics
- Comprises **10** complex areas
- Subject Matter Experts across 9 CDER Offices
- Average time from NDA approval to PSG posting has gone from **~2.5 years in 2017** to less than **~1.5 years in GDUFA III**

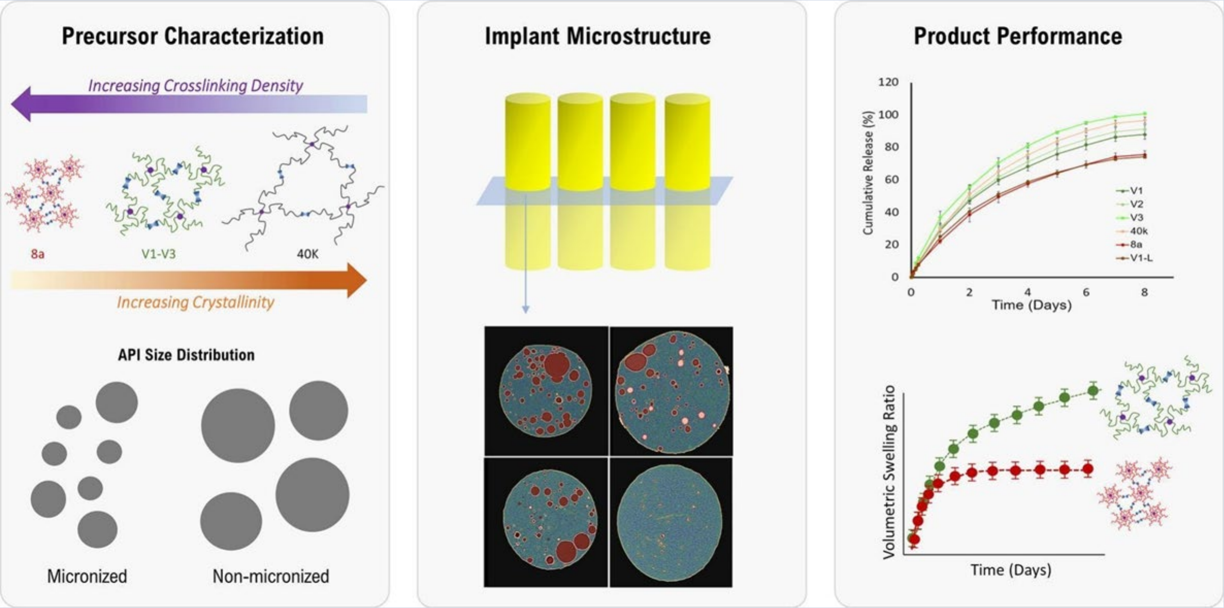
96	**NDAs Triaged**
15	**Research Projects Identified**
65	**PSGs Published**

Example of STT:

DEXTENZA® (dexamethasone ophthalmic insert) 0.4 mg, for intracanalicular use

Research identified to understand impact of polymer variations on hydrogel structure and product performance. VandenBerg, MA., et al. Int J Pharm (2025): 125959

Planned PSG posting is Nov 2025, per FDA's website: *Upcoming Product-Specific Guidances for Generic Drug Product Development*



Efforts and Areas for Global Harmonization of PSG Recommendations

FDA conducts research and solicits feedback for PSG development and revision, including sharing knowledge and aligning recommendations with other regulatory agencies where appropriate.

- Discussions on harmonization of product specific recommendations with other global agencies
    - Generic Drug Cluster increases scientific understanding and global alignment among leading regulatory agencies which includes European Medicines Agency, Health Canada, the UK's Medicines and Healthcare products Regulatory Agency, Swissmedic, Australia's Therapeutic Goods Administration, and the Israeli Ministry of Health.
- ICH efforts, such as the M13 series; M13A *Bioequivalence for Immediate-Release Solid Oral Dosage Forms* (Oct 2024) and associated revision to over 800 PSGs.
    - M13A streamlining when fasted vs fasted and fed BE studies are needed has an estimated industry savings of 50 million dollars per year (based on 200 ANDA approvals in FY2024 for products impacted by M13A recommendations)
- Ultimately FDA’s recommendations are based on FDA regulations and a science-based evaluation of the data available to FDA.

PSG Revisions

Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Iron Sucrose

August 2025

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

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Active Ingredient: Iron sucrose

Dosage Form: Injectable

Route: Intravenous

Strengths: EQ 50 mg iron/2.5 mL (EQ 20 mg iron/mL), EQ 100 mg iron/5 mL (EQ 20 mg iron/mL), EQ 200 mg iron/10 mL (EQ 20 mg iron/mL), EQ 65 mg iron/3.25 mL (EQ 20 mg iron/mL), EQ 75 mg iron/3.75 mL (EQ 20 mg iron/mL)

Recommended Studies: One in vivo bioequivalence study with pharmacokinetic endpoints, one in vitro bioequivalence study with particle size distribution, and comparative characterization studies

In vivo bioequivalence study with pharmacokinetic endpoints:

1. Type of study: Fasting
   Design: Single-dose, randomized in vivo study
   Strength: EQ 100 mg iron/5 mL
   Dose: 100 mg iron
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: The products should be administered undiluted as a slow intravenous injection dose of 100 mg over 5 minutes for both the test (T) and reference standard (RS) products at the same rate. The in vivo bioequivalence study may be conducted using either a parallel or a crossover design. A replicate crossover study may be an appropriate alternative to the parallel or nonreplicated crossover studies. Bioequivalence can be demonstrated by following either the approaches in Option 1 or Option 2.

Recommended Mar 2012; Revised Nov 2013, Sep 2021, Aug 2025

FDA's revisions to a PSG often reflect more streamlined recommendations, additional BE options for greater development flexibility, and improved clarity.

- In 2022, FDA updated PSG formatting to clearly distinguish the type and number of studies recommended. In general,
  - Studies that include a statistical assessment criteria are listed as BE studies[¥] in the PSG, such as:
    - In vitro particle size distribution that include a statistical criterion (e.g., population bioequivalence assessment of D50 and SPAN)
    - In vitro release rate testing with a statistical assessment (e.g., f2 analysis)
  - Studies listed as 'characterization' should be comparable to the reference standard but do not include a statistical criterion.
  - This general framework (i.e., if the study includes a statistical criterion) can be applied to PSGs that have not been updated to the current formatting.

¥ See draft guidance for industry, *Handling and Retention of Bioavailability BA and Bioequivalence BE Testing Samples* (March 2024). Typically, BE sample retention (21 CFR § 320.38) applies to studies listed as BE studies in a PSG and not to studies listed as characterization tests. A controlled correspondence can be submitted for application specific questions.

Peptide Products: Active Ingredient Sameness

Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Glucagon

August 2023

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Active Ingredient:	Glucagon
Dosage Form:	Solution
Route:	Subcutaneous
Strengths:	0.5 mg/0.1 mL, 1 mg/0.2 mL
Recommended Studies:	Comparative characterization studies to support active pharmaceutical ingredient (API) sameness and request for waiver of in vivo bioequivalence study requirements. For test and reference products with an auto-injector presentation two in vitro bioequivalence studies on delivered volume and extended needle length; and supportive characterization studies on trigger force and ejection time.

Recommendations to support API Sameness and Impurity Assessment:

In addition to ensuring API sameness (i.e., same primary sequence and physicochemical properties) for the drug substance, it is recommended to conduct the following comparative analyses of the proposed generic glucagon and the reference listed drug (RLD) product on no less than three batches of the proposed drug product tested on or near release and at the end of the proposed shelf life and no less than three batches of the RLD aged prior to expiry, after aging under conditions consistent with the label storage conditions:

1. Secondary structure
2. Oligomer/aggregation states: oligomer/aggregation propensity and the nature of the aggregates formed for the proposed product should be similar to that of the RLD
3. Biological activities[1]
4. API-related impurity profile comparison: new impurities found in the proposed generic drug product but not in the RLD and impurities found at a significantly higher level in the proposed generic drug product than in the RLD, should be identified. If upon Agency assessment, an impurity is identified that has the potential to increase the immunogenicity risk, further immunogenicity assessments or studies may be required
5. Comparative study demonstrating comparable innate immune response risk of the proposed product and RLD

- For intended generics for which a PSG with active ingredient sameness recommendations or the ANDA peptide guidance* applies, comparative characterization of the following for the proposed product and RLD is generally recommended using orthogonal analytical methods
  - Primary sequence and physicochemical properties
  - Secondary structure
  - Oligomer/aggregation states
  - Biological activities

* FDA Guidance for Industry *ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin* (May 2021)

Peptide Products: Active Ingredient Characterization and Comparability Studies

- Characterization:
  - Characterization of drug substance primary peptide structure and physicochemical properties
    - Provide evidence to ensure the identity, strength, quality, and purity of the peptide drug substance
    - Characterization of primary peptide structure performed against the RLD label claim
    - DMF can be referenced for the active ingredient characterization information
- Comparability:
  - Provide evidence to ensure the peptide higher-order structure, oligomer/aggregation states and biological activities *in the proposed finished drug product* are comparable to those of the RLD
    - Comparability studies are performed with proposed product and RLD samples
- These analytical studies are important as supporting evidence that the proposed product has the same therapeutic effect as the RLD and are an integral part of the assessment and mitigation of immunogenicity risk
- Not all studies needed for all peptide products, e.g., smaller peptides may not have significant higher-order structure, or propensity to aggregate

Peptide Products: Active Ingredient Characterization and Comparability Studies

FDA

	Attribute	Examples of Characterization/ Comparability Studies	Examples of Methods
DS	Primary sequence and physicochemical properties	Primary peptide structure/sequence Solubility as a function of pH, hygroscopicity, log P, isoelectric point (pI), specific optical rotation	IR, UV, NMR, CD Spectroscopy, Mass Spectrometry, Amino Acid Analysis, L- and D- Amino Acid Content, Amino Acid Sequencing (Edman Degradation and/or HRMS/MS)
DP	Higher Order Structure	Secondary: α-helix, β-sheet, random coil, unordered Tertiary: overall monomer structure	Secondary: Far-UV CD, FTIR, Raman Spectroscopy Tertiary: Near-UV CD, Intrinsic Fluorescence DSC (Differential Scanning Calorimetry), NMR
	Oligomer/ Aggregation States	Ordered/disordered Reversible/irreversible, Soluble/insoluble	Light Scattering: SEC-UV/MALS, CG-MALS, DLS Analytical Ultracentrifugation: SE-AUC, SV-AUC Gel Electrophoresis: SDS-PAGE, Native Field Flow Fractionation: AF4 MFI (Micro-Flow Imaging)
	Biological Activities	Therapeutically relevant bioassay	Glucagon Bioidentity Tests USP⟨123⟩

If recommended studies are not appropriate for a proposed peptide product, justification with supporting data may be provided to support an alternative approach

Peptide Products: Comparative Studies of Oligomerization State

- Oligomers
  - Inherent self-association of multiple active ingredient molecules in solution generally in an *ordered, reversible* manner, e.g., dimer, trimer, hexamer, octamer, etc.
  - Dependent on factors such as the formulation composition (Q1/Q2), active ingredient concentration, temperature
  - Desired property hence important for demonstration of *Active Ingredient Sameness*: Demonstrate oligomer states present in formulated solution are comparable to those of the RLD in terms of identity and relative levels
- Analytical method examples
  - Sedimentation Velocity/Sedimentation Equilibrium Analytical Ultracentrifugation (SV-AUC/SE-AUC)
  - Composition Gradient-Multi-angle Light Scattering (CG-MALS)
  - Asymmetric Flow Field-Flow Fractionation (AF4)

Peptide Products: Comparative Studies of Aggregation State

- Aggregates
  - Association of multiple active ingredient molecules generally in a *disordered, sometimes irreversible* manner as soluble/insoluble species, e.g., dimer, trimer (may exist as sub-visible or visible particles)
  - Undesired property hence important for *Routine Quality Control*: Demonstrate that levels of aggregates found in the proposed product are the same as or less than those of the RLD and that the identity of any aggregates present are comparable to the RLD
- Analytical method examples
  - Size Exclusion Chromatography: commonly used for routine control; limits may be qualified using comparative RLD data
  - Micro-Flow Imaging: characterization of solid-phase aggregates

Colloidal Iron Carbohydrate Products: Comparative Physicochemical Characterization

Contains Nonbinding Recommendations

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Active Ingredient:	Iron sucrose
Dosage Form:	Injectable
Route:	Intravenous
Strengths:	EQ 50 mg iron/2.5 mL (EQ 20 mg iron/mL), EQ 100 mg iron/5 mL (EQ 20 mg iron/mL), EQ 200 mg iron/10 mL (EQ 20 mg iron/mL), EQ 65 mg iron/3.25 mL (EQ 20 mg iron/mL), EQ 75 mg iron/3.75 mL (EQ 20 mg iron/mL)
Recommended Studies:	One in vivo bioequivalence study with pharmacokinetic endpoints, one in vitro bioequivalence study with particle size distribution, and comparative characterization studies

Comparative characterization studies:

The proposed T product should be qualitatively (Q1)[2] and quantitatively (Q2)[3] the same as the reference listed drug (RLD). Comparative physicochemical characterization of the T and RS products should be conducted with orthogonal analytical methods.[4] The comparative studies should be performed on a minimum of three batches of the T[5] product and three batches of the RS product and should include:[6]

- Physicochemical properties of the drug product:
  - Particle size and size distribution[7]
  - Particle morphology
  - Zeta potential at pH values spanning the acidic, neutral, and basic ranges
  - Molecular weight determination by size-exclusion chromatography (SEC)[8]
  - Interaction between polynuclear ferric oxyhydroxide core[9] and sucrose
  - Stoichiometric ratios of iron, carbohydrate, and relevant components, before and after dialysis/ultrafiltration
  - Fe(III) to Fe(II) reduction potential and reduction kinetics
- Polynuclear ferric oxyhydroxide core characterization:
  - Core size and morphology
  - Polynuclear ferric oxyhydroxide crystalline structure and environment
  - Magnetic properties
- Labile iron determination under physiologically relevant conditions. The tests may be conducted using an in vitro hemodialysis system,[10] the catalytic bleomycin assay of spiked human serum samples,[10,11] spectrophotometric measurement of Fe reduction, chelatable iron assay,[12] or other methods that are adequately validated.

- Physicochemical properties of the drug product:
  - Particle size and size distribution
  - Particle morphology
  - Zeta potential at pH values spanning the acidic, neutral, and basic ranges
  - Molecular weight determination by size-exclusion chromatography (SEC)
  - Interaction between polynuclear ferric oxyhydroxide core and sucrose
  - Stoichiometric ratios of iron, carbohydrate, and relevant components, before and after dialysis/ultrafiltration
  - Fe(III) to Fe(II) reduction potential and reduction kinetics
- Polynuclear ferric oxyhydroxide core characterization:
  - Core size and morphology
  - Polynuclear ferric oxyhydroxide crystalline structure and environment
  - Magnetic properties

Colloidal Iron Carbohydrate Products: Comparative Physicochemical Characterization

	Property	Common Tests
Whole particle	Equivalence in stoichiometric ratios of iron, free and bound carbohydrate and other relevant components	Iron and carbohydrate assay, elemental analysis
	Molecular weight distribution (Mw, Mn, and Mw/Mn)	SEC, AUC or GPC
	Particle size distribution	DLS and AFM
	Particle morphology	AFM
Iron core	Iron core size and morphology	TEM, XRD, SAXS
	Crystallinity	Mossbauer, Raman, XRD
	Iron environment	Mossbauer, EPR, UV-Vis
	Fe^{3+} to Fe^{2+} reduction potential and Fe (II) content	Polarography, Cerimetric titration
	Magnetic properties	VSM, SQUID
Carbohydrate	Carbohydrate composition and carbohydrate-iron core interaction	FT-IR, thermal analysis
	Surface properties	Zeta potential
	Characterization of carbohydrate	NMR, SEC

Refer to presentation titled "Comparative Physicochemical Characterization of Iron Products" by Dahui Liu at FDA 8th Annual Advancing Generic Drug Development: Translating Science to Approval 2025 Virtual Workshop, October 7-8, 2025 for more information on selection of orthogonal methods for characterization of this product class.

P. Zou, K. Tyner, A. Raw, S. Lee, AAPS J. 2017, 1359-1376.

Notable Examples of Complex Product Approvals

	Drug Product Name	ANDA number	Applicant	Approval Date
Peptides	Liraglutide Injection (N206321, SAXENDA)	A214568	TEVA PHARMS	08/27/2025
		A217234	ORBICULAR PHARMACEUTICAL TECHNOLOGIES PVT LTD	09/11/2025 (Tentative Approval)
	Liraglutide Injection (N022341, VICTOZA)	A215503	HIKMA	12/23/2024
		A218115	NANJING KING FRIEND	04/02/2025
		A215421	LUPIN LTD	07/22/2025
	Teriparatide Injection (N021318, FORTEO)	A208569	TEVA PHARMS USA	11/16/2023
		A211097	APOTEX	11/16/2023
	Glucagon for Injection (N020928)	A208086	AMPHASTAR PHARMS INC	12/28/2020
		A204468	MYLAN LABS LTD	12/12/2024
		A214457	LUPIN LTD	07/22/2025
		A218813	CIPLA	09/15/2025
Colloidal Iron Carbohydrates	Iron Sucrose Injection (N021135, VENOFER)	A208977	INTL MEDICATION SYS	08/08/2025
		A212340	SANDOZ	08/08/2025
		A212559	MYLAN LABS LTD	08/08/2025

Closing Thoughts

- Complex products ANDA submissions and approvals have increased over the last 20 years and currently represent 12-19% of annual ANDA submissions and approvals.
- Complex product ANDAs are more likely to have major BE and/or major Drug Product deficiencies than non-complex products if issued a Major Complete Response Letter in the 1st Review Cycle.
- FDA's proactive STT program, in response to our GDUFA III commitments, has reduced the time from complex product NDA approval to PSG posting by identifying and directing research needs.
- Revisions to PSGs commonly reflect more streamlined recommendations, BE options for greater development flexibility, and improved clarity.
- Use of orthogonal methods is recommended to reduce uncertainty in comparative characterization of a particular attribute
- Selection of orthogonal methods should be suitable to characterize the attribute under consideration
- Methods should be validated as necessary and demonstrated to be suitable for their intended use

Thank You